Modified Venezuelan Kaolin as Possible Antacid Drug

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Abstract: A Venezuelan clay conformed mainly by kaolin was modified hydrothermically using sodium carbonate solutions at different concentrations: 0.5, 1.0, 1.5 and 2.0 M. The synthesized solids were characterised using different techniques such as: X ray diffraction (XRD), infrared (FT-IR) and BET surface area to determine the textural properties from original and modified clay. Finally, all solids were tested in the presence of synthetic gastric juice (HCl + pepsin) to determine its neutralization capacity. The results showed that modified clays were more active than original clay. The activities of these modified materials increase, when the concentration in sodium carbonate with which these materials were treated, is increased. On the other hand, it was observed a small interaction among the modified clays and pepsin molecule; this interaction was also determined to a commercial compound with antacid properties. The interaction was related to the adsorption of pepsin molecule on the surface of solids, which do not change its chemical properties. These new antacid materials are interesting because they can be very cheap and effective.

Key words: Venezuelan clays, kaolin, sodium carbonate, antacid, pepsin

INTRODUCTION

Clays are natural minerals generated by decomposition of rocks under action of the wind and water millions of years ago. The clay minerals are part of a general but important group within the phyllosilicates that contain large percentage of water trapped between the silicate sheets[1]. Clays are rarely found separately and are usually mixed not only with other clays but also with microscopic crystals of carbonate, feldspars, mica and quartz. They can be divided into four major groups: kaolin, montmorillonite/smectite, illite and chlorite. There are many important uses and considerations of clay minerals; they are used in manufacturing, drilling, construction, paper production and in pharmaceutical formulations.

As a medical product, they can be employed as excipients or as active ingredient fundamentally due to its high specific area, sorptive capacity, rheological properties, chemical inertness and low or null toxicity for the patient[2].

Some of these pharmaceutical properties associated to clays can be used against stomach acidity.

Hyperacidity is referred to gastric disturbances characterised by an abnormal increase in the hydrochloric acid concentration in the stomach and a consequent decrease in pH. Such gastric disturbances are commonly treated by means of so-called antacid, which are supposed to neutralize, to some extent, the excess of hydrochloric acid in the gastric content[3-5].

The aim of this research was to evaluate the capacity as antacid of hydrothermally modified kaolin with sodium carbonate solutions. The kaolin used is from Guárico State in Venezuela and its ores have previously been characterised. Possible interactions among the modified clays and pepsin enzyme were also determined. The results showed a high capacity of neutralization of HCl from gastric juice by modified kaolin.

MATERIALS AND METHODS

Hydrothermal transformation of kaolin: The kaolin, had previously been quantitatively and qualitatively analyzed (Table 1). Then, this kaolin was hydrothermally transformed according to a previously reported procedure[6,7]. Portions of kaolin were placed in contact

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Table 1: Oxide-form composition of the original kaolin

	SiO_2	Al_2O_3	Fe_2O_3	CaO	MgO	Cr_2O_3	K_2O	TiO_2
Original clay	53.98	16.96	7.16	≈ 1	≈ 1	≈ 1	≈ 1	≈ 1

under mechanical agitation with: 0.5, 1.0, 1.5 and 2.0 M sodium carbonate solutions using a solid-liquid ratio of 1: 4 at 25°C, for 24 h at first; in a second stage, the slurry was exposed at 100°C per 1 h at atmospheric pressure in reflux condition. Finally, the solids were centrifuged and dried.

Characterisation: Solids were characterised by XRD, BET surface area and FT-IR. XRD studies were conducted using a Phillips PW 3442 diffractometer with a CoKα radiation (1.54060 Å) for crystalline phase detection between 4 and 70° (2θ) and the patterns obtained were compared with JCPDS data files. Physisorption measurements were performed with a Beckman Coulter SA 3100 instrument; BET surface areas were determined by nitrogen adsorption at -196°C with an Ar/N₂ ratio of 70/30. The presence of functional groups and evaluation of the solids purity were achieved by FT-IR; spectra were recorded in a Perkin-Elmer 283 spectrometer in a range of 4000-200 cm⁻¹. Samples were prepared dissolving the solids in KBr to form a thin pastille.

Antacid capacity: The antacid capacity of the modified clays was evaluated using the methodology previously reported[4,7]. Solids were tested in the presence of synthetic gastric juice (HCl + pepsin, pH≈1.5), contacting 50 to 1000 mg of the solids with an aliquot of 20 mL of synthetic gastric juice. This dispersed solution was shaken during 1 h at 37°C to simulate the rhythmical movements of the stomach. The solution was then filtered and an aliquot of 10 mL was potentiometrically titrated with previously standardized NaOH using an Acumment AB15 pH meter with glass electrode and a sensitivity of ±0.05 pH units. The pH of the solutions was evaluated in two ways: (a) directly using the previously calibrated pH meter, named "experimental pH", (b) the pH determined by the potentiometer titration (theoretical pH=-log[H⁺]), where [H⁺] corresponds to the free protons concentration determined in the acid-base titration.

The interaction solid-pepsin was measured by UV-visible spectroscopy by means of an HP 8452A with diode arrangement, using a filtered aliquot from modified kaolin mixed with the synthetic gastric juice. The spectrum was recorded between 200 and 400 nm. Spectra were taken before and after contacting the solids with the synthetic gastric juice. Finally, FT-IR spectroscopy was applied to solids after the interaction with the synthetic gastric juice.

Previous to the analysis by FT-IR the soils were washed with abundant distilled water.

RESULTS AND DISCUSSION

Figure 1 shows the X-ray diffractograms of kaolin after and before contact with 2 M sodium carbonate solution. The XRD results indicate that kaolin is the main phase but other phases in minor proportion, such as vermiculite, quartz, palygorskite and muscovite, were also identified in the clay mineral[8]. When the clay was treated with the sodium carbonate solution, negligible variations were observed in the relative intensities of the peaks and their interplanar distances; however, new peaks were observed. The most intense were identified as: $Na_3H(CO_3)_2.2H_2O/3Na_2O.4CO_2.5H_2O$, $Na_3H(CO_3)_2.2H_2O$ $Na_2Ca(CO_3)_2.2H_2O$ and the first phase was formed during the Ca^{2+} reaction from kaolin with Na_2CO_3. Under this condition, it is possible to precipitate the calcium salt. The other phases correspond to sodium carbonate salts formed during the basic hydrolysis reaction of carbonate anion:

$$CO_3^{2-} + H_2O \leftrightarrow HCO_3^- + OH^- \qquad (1)$$
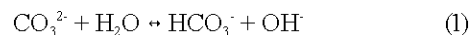
All calcium and sodium salts formed during the hydrothermal reaction remain occluded between layers of clay. These occluded salts can be used as "carbonate pump" allowing the dosage of carbonate against the acidity.

Figure 2 shows IR spectra of original and modified kaolin after being treated with sodium carbonate solutions. For the original kaolin, bands placed between the region of 3702 and 3621 cm⁻¹ region correspond to OH stretching (hydroxyl sheet); the band observed at 1639 cm⁻¹ present in all spectra, corresponds to water molecules occluded inside the clay sheets. Bands in the 1111-1004 cm⁻¹ region correspond to SiO stretching. The band at 912 cm⁻¹ belongs to OH deformation and those ones placed at 794-420 cm⁻¹ were identified as mixed SiO deformations and octahedral sheet vibration[8]. Bands corresponding to other phases were negligible and they could not be identified in the spectra. No relevant variation in the frequencies of the assigned bands were observed after hydrothermal treating applied to clays,

Table 2: Surfaces areas determined for the original and modified kaolin

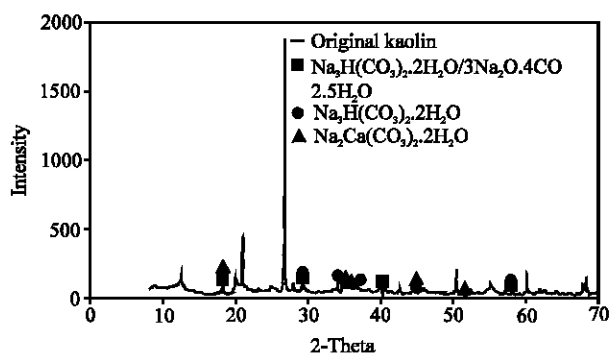| Kaolin	Surface area (m² g⁻¹)
Original kaolin	34
0.5 M	25
1.0 M	24
1.5 M	21
2.0 M	19

Fig. 1: X-ray diffractograms of modified kaolin with 2 M sodium carbonate solution. The symbols represent some phases determined after the hydrothermal reaction
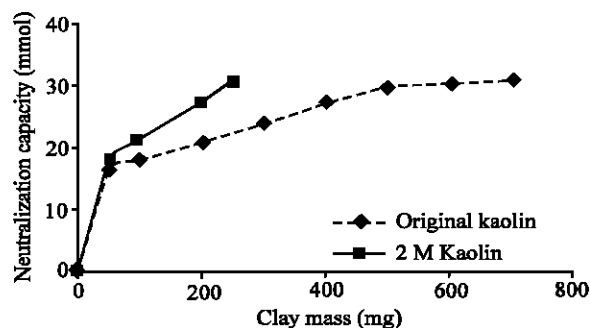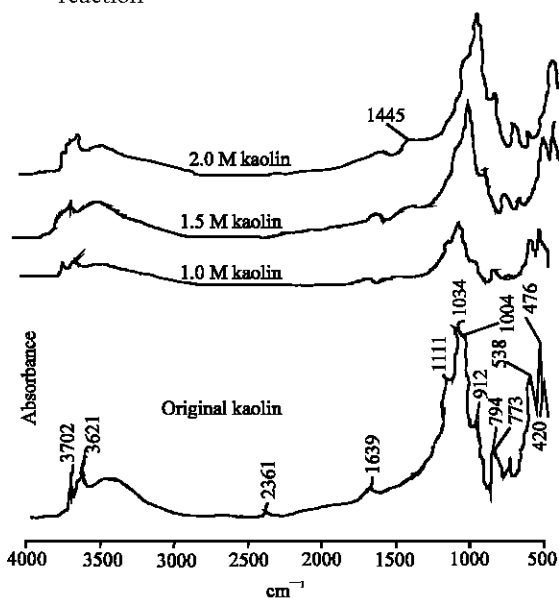

Fig. 2: IR spectroscopy spectra recorded before and after hydrothermal treating applied to original kaolin using different sodium carbonate solutions

but a new band appears at $1444 cm^{-1}$ which corresponds to carbonate molecules occluded between sheets of clay[9].

It can be observed, the surface areas of the samples decrease, in comparison with the original clay, when sodium carbonate concentration is increased (Table 2). This fact corroborates the effective blockage of the porous of the clay by the presence of precipitated carbonate salts. Of course, if the sodium carbonate concentration used is very high, it is possible a major blockage of porous; however, according to ours experiences, the blockage of porous was possible in a high extension, using diluted sodium carbonate solutions.

Fig. 3: Neutralization capacity (mmol) for original and 2 M kaolin in the presence of synthetic gastric juice

Figure 3 shows the results from antacid capacity using the original and modified (2 M) clay at different masses. These studies were essayed to a synthetic gastric juice. As it can be observed, the neutralization capacity increases with the kaolin mass for both clays, but the neutralization capacity is superior in the modified clay than original one, due to the carbonate salts inside the framework. Using only 250 mg of the modified clay, it is possible to achieve an excellent antacid capacity in comparison to the original clay, which needs a high dose (>400 mg). The neutralization capacity for the original clay is generated by calcium, iron and other cations coming from the composition of the clay, just as it is indicated by its chemical composition. These results obtained with the original clay are very interesting because they show higher neutralization capacity in comparison to other minerals such as clinoptilolites zeolites[6]. However, the antacid capacity obtained with the original and modified clay is not definitive because the proteolytic role of pepsin must be evaluated according to the stomach pH. At a high value of pH (>5), this enzyme can denature. For this reason, other methods based on pH and not only must the titration technique method be employed[6,7].

As an example, the pH solution as a function of kaolin mass for 0.5 M kaolin (Fig. 4). In general, the behaviour of all the kaolins essayed was very similar, even that of the original clay used as reference: the theoretical and experimental pH increase as the weight of the studied solid increases, just as it was explained above. The experimental pH values were higher than that of the theoretical ones. The difference observed could be due to the way in which both pH values were determined. The experimental pH values were determined using a glass electrode which is only sensitive to the amount of free protons in the synthetic gastric juice; while, the theoretical pH values were determined using the expression $pH = -\log[H^+]$ which is applied to the results
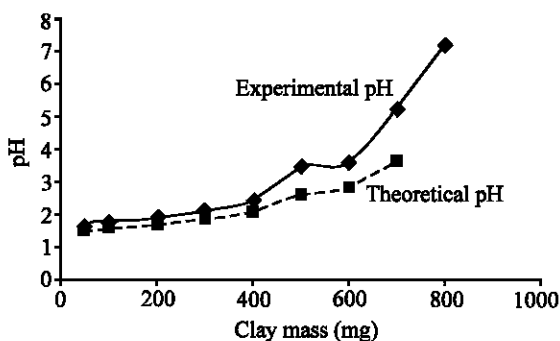
Fig. 4: Experimental and theoretical pH determined for 0.5 M kaolin in the presence of synthetic gastric juice
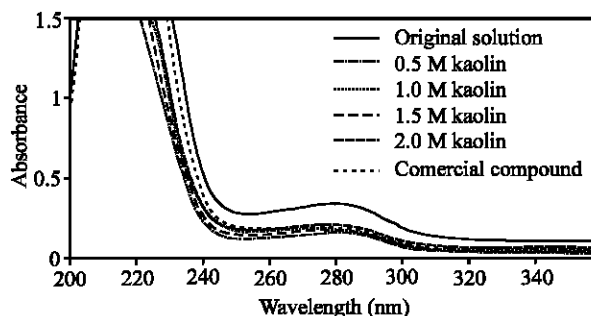

Fig. 6: UV-visible absorbance spectra recorded for synthetic gastric juice before and after the contact with modified kaolin and a commercial compound
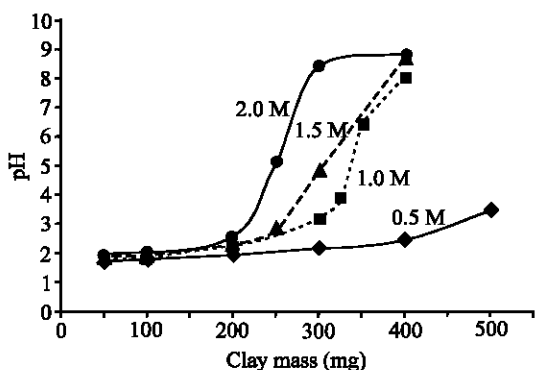

Fig. 5: Experimental pH in function of different clay mass for all modified kaolin with sodium carbonate solution in the presence of synthetic gastric juice
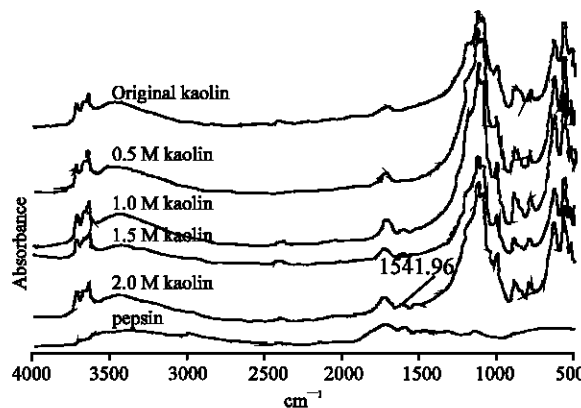

Fig. 7: FT-IR spectroscopy spectra recorded for modified kaolin before the contact with pepsin solution

of the acid-base titrations. However, during the neutralization procedure with NaOH, other ions or species such as potassium, magnesium, calcium, iron and pepsin enzyme along with free proton ions can interact with the OH⁻ groups making the calculated pH lower than the experimental one. Rivera *et al.*[6,7] reported similar results. These authors suggest the use of the experimental pH as the more effective way to determine the neutralization capacity of zeolites.

According to the previous explication, we determined the experimental pH versus different amount of mass of modified kaolin (Fig. 5). The results show a major increase of pH as the concentration of sodium carbonate increases in the treated kaolin. Using 250 mg of 2 M kaolin, it is possible to achieve a pH between 3 and 4 (optimum pH) while it is necessary 500 mg of 0.5 M kaolin to achieve the same pH values. Lesser doses than the one used for 0.5 M kaolin are necessary for 1.0 and 1.5 M kaolin. Of course, the neutralization capacity is associated to a major content of carbonate inside kaolin. However, we do not have a clear explication why there are not significant

differences in relation to pH values when quantities lower than 200 mg (for all modified kaolin) are tested in the presence of synthetic gastric juice. Maybe, the carbonate salt inside kaolin is "pumped up" slowly to lower pH values.

Similarly, it is well known that the enzymatic function of the pepsin is highly influenced by the pH of the gastric juice of the stomach. The extreme acidity or basicity of the gastric juice denaturalize the enzymatic activity of the pepsin, which shows its higher activity at a pH=2. At pH=5 the enzyme starts to deactivate; from a pH=7, the enzyme irreversibly lessen its activity[10]. From Fig. 5, it is observed that doses as small as 250 mg of 2.0, 1.5 or 1.0 M kaolin are enough to reach the optimum pH necessary to control the hyperacidity of the stomach and to maintain a high enzymatic activity of the pepsin. Quantities higher than 250 mg of 2 M or 350 mg for 1.0 and 1.5 M kaolin are not recommended because, although they show extraordinary therapeutic properties on the control of the acidity, high doses reduce the enzymatic activity of the pepsin.

The use of low doses of modified clays to produce effective antacid is a high achievement since costs of production will be lower. Contrary to the results observed with antacids produced from natural zeolites by hydrothermal treatment with Na_2CO_3, as is the case for clinoptilolite zeolite, higher doses (>400 mg) are needed to control hyperacidity[6] .

To determine the interaction of the synthesized solids with pepsin, variable quantities of modified clays, depending on its antacid activity (pH between 3 and 4), were put in contact with the synthetic gastric juice. Figure 6 shows the UV-visible spectra of solutions from modified kaolin before and after interaction with acidic solution. The original acid solution with pepsin, without interaction with any solid, showed a maximum at 272 nm and a minimum at 250 nm. After interaction with the modified clays, a small decrease in the maximum absorbance of the pepsin was observed for all modified clays. This small decrease is probably due to higher surface areas from kaolin that favours a stronger interaction with the enzymes. However, no solid showed a different spectrum to that of the original pepsin. Evidently, there was not a chemical reaction between the enzyme and the solids, but only some adsorption occurs on the surface of them. For comparison, a commercial antacid formulated with hydrotalcite (Baytalcid®) was tested. The results showed the same interaction with the pepsin molecule (Fig. 6). It can be concluded that this interaction is normal when formulated antacid is placed in contact with the pepsin.

The interactions pepsin-solid were also determined by FT-IR spectroscopy. Figure 7 shows the spectra of the solids after the contact with the synthetic gastric juice. These solids were washed three times with abundant distilled water just before the FT-IR spectrum was recorded. For comparison with original clay, a small new band at 1542 cm^{-1} was observed, which is associated to carbonyl groups from pepsin molecule. These results confirm the adsorption of pepsin on the solids observed by UV-visible spectra.

Finally, it is possible to use these modified clays as effective antacid. They could be very economical in comparison to other natural antacids. Together with all what has been mentioned before, it is very well known that clays have a variety of pharmaceutical applications. Those medical properties, in combination with an antacid effect, make this material a good multipurpose medical drug.

It was demonstrated that it is possible to modify kaolin with sodium carbonate solution in different concentrations. These modified solids can be used as effective antacid drugs. The effectiveness of these synthesized medicaments depends on the concentration of sodium carbonate used; a major concentration in these solutions generates an increase in the effectiveness of the drugs. The neutralization test shows that lower doses used, such as, 250 mg can be used to reach the normal pH of the stomach. The pH achieved using these solids do not denaturalize the pepsin. The interactions pepsin-clay resulted to be very small and they were not reactive to pepsin molecule. This results show that it is possible to use these carbonated clays as effective antacids.

REFERENCES

1. Konta, J., 1995. Clay and man: clay raw materials in the service of man. Appl. Clay Sci.,10: 275-335.
2. Carretero, M., 2002. Clay minerals and their beneficial effects upon human health. A review. Appl. Clay Sci., 21: 155-163.
3. Beers, M. and R. Berkow, 1999. The merk manual. 10th Edn. Madrid. España, pp: 254-255.
4. Linares, C.F., S. Sánchez, C. Urbina de Navarro, K. Rodríguez and M.R. Goldwasser, 2004. Use of carbonated cancrinite type zeolites and hydrotalcite as antacid drogue. Acta Cien. Vene. (In press).
5. Visera, C. and A. López-Galindo, 1999. Pharmaceutical applications of some Spanish clays (sepiolite, paligorskite, bentonite): some preformulation studies. Appl. Clay Sci.,14: 69-82.
6. Rivera, A., G. Rodríguez-Fuentes and E. Altshuler, 1998. Characterization and neutralizing properties of a natural zeolite/Na_2CO_3 composite material. Microporous Mesoporous Mater., 24: 51-58.
7. Rivera, A., G. Rodríguez-Fuentes, I. García and M. Mir, 1996. Preparación y caracterización de un material zeolítico con propiedades básicas. E. Herrero, O. Anunziata and C. Pérez (Eds.), Actas de XV. Simposio Iberoamericano de Catálisis. Córboba. Argentina, 3: 1521-1526.
8. Van Olphen, H. and J.J. Fripiat, 1979. Data Handbook for Clay Materials and Others Non-metallic Minerals. Edit. Pergamon Press. New York, USA., pp: 285-327
9. Linares, C.F., S. Madriz, M.R. Goldwasser and C. Urbina de Navarro, 2001. A novel method for the synthesis of cancrinite type zeolite. Stud. Surf. Sci. Catal., 135: 331-339.
10. Fordtran, J.S., S. Morawski and Ch.T. Richardson, 1973. *In vivo* and *in vitro* evaluation of liquids antacids. New Engl. J. Med., 288: 923-928.